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Considering the New REMS Legislation of the 2007 Amendments

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This paper is submitted in satisfaction of the course requirement.

## **Abstract**

On September 27, 2007, the Congress passed new amendments to the Food, Drug and Cosmetic Act. These amendments contained numerous changes to the act aimed at addressing the current needs for food, drug, and cosmetic safety. Yet, arguably one area of that law that could potentially have the greatest impact on the safety of many Americans is that containing elements regarding risk analysis. Sections 505-1 and 505(o) contain new rules on how drugs can be regulated in the post-market phase. Key to these rules is the initiation of a system of Risk Evaluation and Mitigation Strategies (REMS). This new system empowers the FDA to require companies to create a plan to address risk concerns of drugs upon initial approval and in the post-approval stage. From the data outlined in this work, it appears that while this law will certainly give the FDA more formal power to force drug companies to investigate and prevent risks, it seems unlikely that the initiation of REMS will lead to radically different behavior on the part of the FDA. The REMS legislation will most likely be another iteration of the FDA's ongoing attempt to ensure that companies balance risks and benefits. Instead of serving as a means to stifle benefits for fear of risks, the law would most likely result in drugs with significant risks being made available to the subpopulations that most need them.

## **Introduction**

On September 27, 2007, the Congress passed new amendments to the Food, Drug and Cosmetic Act. These amendments contained numerous changes to the act aimed at addressing the current needs for food, drug, and cosmetic safety. Yet, arguably one area of that law that could potentially have the greatest impact on the safety of many Americans is that containing elements regarding risk analysis. Sections 505-1 and 505(o)

contain new rules on how drugs can be regulated in the post-market phase. Key to these rules is the initiation of a system of Risk Evaluation and Mitigation Strategies (REMS). This new system empowers the FDA to require companies to create a plan to address risk concerns of drugs upon initial approval and in the post-approval stage. In the following work, several factors in reference to the REMS legislation will be considered: (1) how is this new REMS system situated within the FDA's policies on risk assessment, (2) how is this new REMS system situated within the history of occurrences that have implicated FDA's risk assessment policy (3), what were some of the concerns over FDA's drug policies in the time immediately before the 2007 amendments, (4) what are the actual provisions of the REMS system within the law, and (5) what will be the likely impact of the new REMS requirement on the ways in which drug companies operate in the United States.

## **History of Risk Assessment at the Food and Drug Administration**

### *1962 Amendments*

In regard to FDA statutes, risk assessment began with the 1962 Amendments which for the first time made effectiveness a pre-market requirement for new drugs (Farley). For the first time, it was not sufficient for drug companies to just show that a drug was safe; they now had to fully analyze its risks and its benefits by relating its safety to its effectiveness (FDA Consumer). To that end, the 1962 amendments required that drug firms send adverse reaction reports to the FDA and that drug advertising to physicians had to be comprehensive. Also, drug companies had to receive prior clearance for human trials, drug advertising, and labeling (FDA Review).

According to data, the 1962 amendments had an effect on drug approval in the United States. It soon became evident that efficacy was harder to prove than safety since efficacy depended on the nature of the patients and the similar drugs on the market (i.e. was the new drug more effective than the drugs already present) (FDA Review). Thus, one of the major outcomes of the Kefauver-Harris amendments was that it took longer to get drugs to market; the expense and time required for extensive tests required to prove efficacy and the wait time for FDA approval limited the number of drugs that were ready for market (FDA Review).

This change in the drug approval rate was borne out in a study conducted by Peltzman (1973). After reviewing the introduction of drugs before and after the 1962 amendments, he concluded that:

[T]he [Kefauver-Harris] amendments have produced a substantial decline in drug innovation since 1962. This could have produced net benefits if the impact of the decline had been highly selective against ineffective drugs and preamendment expenditures on ineffective drugs and preamendment expenditures on the ineffective drugs had been substantial. Neither condition is consistent with the data. (p. 1089)

Thus, Peltzman concluded that not only was there an overall decline in drug innovation because of the amendments but there was no evidence that the decline was only in ineffective drugs. Based on this data, the Kefauver-Harris amendments had met the unintended goal of sharply restricting the advent of new drugs while not reaching the intended goal of increasing the efficacy of the drugs that made it to market.

*1999 Task Force on Risk Management*

When Commissioner Henney took the post at the FDA in 1998, one of her first orders of business was to initiate a task force to review the FDA's then current system of risk management. In 1999, the task force delivered its report to the FDA (Task). After examining the FDA's policies and speaking to FDA employees, the Task Force recommended that the agency take several actions including:

- “Integrate existing postmarketing information systems so analytic tools, data entry, and editing can be uniformly applied, and all information is readily available to every reviewer.”
- “Enhance and intensify surveillance of newly marketed products.”
- “Enhance clinical and laboratory studies to develop new methods to improve product safety.” (Task)

And in another section called, “Additional Options,” they had several other suggestions including:

- Design, implement, and maintain prospective product use registries (the bulk of support should come from manufacturers).
- Increase resources to conduct focused epidemiological studies when support of these studies by manufacturers is not feasible. (Task)

Thus, well before the 2007 amendments, the FDA had already considered several of the elements evident in the REMS legislation of the 2007 law, including gathering information on post-market surveillance, sponsoring studies based on new safety information and maintaining registries. The task force did not however recommend that

the drug companies should be held to a REMS-like system that required ongoing risk / benefit analysis.

### *2001 Risk Management Plans*

As of 2001, the FDA was also using risk management plans. Risk management plans were used at the initial approval stage and lasted for two years. A review of the General Accounting Office of FDA programs offers a description of the FDA's risk management plans saying:

Under the voluntary program, drug sponsors may develop, and FDA will review, risk management plans for products while the agency reviews the sponsor's NDA or BLA. By adding FDA's postmarket safety team to the drug review process before a new drug or biologic is approved, FDA officials believe that they will obtain better information on the risks associated with the product much earlier in the process and the sponsor will gain helpful feedback on how best to monitor, assess, and control the product's risks .... FDA officials believe that more rigorous safety monitoring of newly approved drugs during the first few years after they are on the market could help to detect unanticipated adverse effects earlier. Historically, the vast majority of adverse effects have been identified in the first 2 to 3 years after a new drug is marketed. (GAO)

Thus risk management plans were voluntary and were designed to help the drug companies to find and address adverse reactions in new drugs.

An example of a risk management plan sheds more light on the FDA's view of the role of risk management plans (Animal). In this plan, the following description of risk management plan appears:

Risk Management is a set of activities that integrates risk assessment results with other information to make decisions about the need for and method of risk reduction (NRC 1994). Risk managers deal with broad social, economic, ethical, and political issues in choosing from a set of options, using the results of the risk assessment and their understanding of those other issues (NRC 1996). FDA risk managers consider relevant public health, scientific, and regulatory issues. The

ultimate goal of risk management is to generate a set of actions that reduce or prevent risks .... (Animal)

This example risk management plan included goals and objectives of the company in order to address and minimize the known risks of their product. The known risks were described in a section preceding the plan called the “risk assessment” (Animal). Then, in the risk management plan, specific actions such as monitoring the effects of the product and consulting with industry experts were outlined to address the known risks.

#### *2004 RiskMAPs*

RiskMAPs were arguably the precursors to the REMS at the FDA. In 2004, the FDA issued guidance on the use of RiskMAPs or Risk Minimization Action Plans (Murphy). According to the guidance, the four goals of a RiskMAP were to: (1) “assess[] the drug’s benefit/risk balance,” (2) “develop[] and implement[] tools to minimize its risks while preserving its benefits,” (3) “evaluat[e] effectiveness and reassess[] the benefit/risk balance,” (4) “mak[e] adjustments to the risk minimization tools to improve further the benefit/risk analysis” (Murphy). In determining whether to consider requesting a riskMAP, the guidance indicated that the best candidates for a riskMAP were drugs for which there was considerable information about their effectiveness and for which the known adverse events linked to them were preventable. The exact wording of the drug characteristics that favored creating a riskMAP were:

- “Nature and rate of known risks versus benefits: Comparing the characteristics of the product’s adverse effects and benefits may help clarify whether a RiskMAP could improve the product’s benefit-risk balance. The



characteristics to be weighed might include the (1) types, magnitude, and frequency of risks and benefits; (2) populations at greatest risk and/or those likely to derive the most benefit; (3) existence of treatment alternatives and their risks and benefits; and (4) reversibility of adverse events observed.”

- “Preventability of adverse effects: Serious adverse effects that can be minimized or avoided by preventive measures around drug prescribing are the preferred candidates for RiskMAPs.”
- “Probability of benefit: If factors are identified that can predict effectiveness, a RiskMAP could help encourage appropriate use to increase benefits relative to known risks.”

Thus, the FDA appeared to have envisioned the use of riskMAPs for drugs with which they were very familiar. These were apparently drugs for which the benefits were well-known including which sub-populations would most benefit from the drug. And the risks were well known including the range of adverse events. Thus, the riskMAPs were specifically focused on targeting the drugs to the most relevant populations and minimizing adverse events. Evidence of this use of risk maps was further seen in two examples in the guidance of prime candidates for a riskMAP which were:

- Opiate drug products have important benefits in alleviating pain but are associated with significant risk of overdose, abuse, and addiction. The Agency recommends that sponsors of Schedule II controlled substances, including Schedule II extended release or high concentration opiate drug products, consider developing RiskMAPs for these products.

- Drugs that provide important benefits, but that are human teratogens would often be appropriate for a RiskMAP to minimize in utero exposure.

These two choices exemplified the importance that the FDA apparently placed on its familiarity with the drugs regulated by riskMAPs. As examples, the FDA chose two drugs that were well known and whose adverse effects were well-known.

Given the fact that the risks of the drugs are well-known, the FDA guidance noted that RiskMAPs were supposed to be composed of specific goals such as: “fetal exposures to Z drug should not occur” (Guidance). The tools that the guidance recommended to meet the goal sets were familiar. There were three categories that the agency noted:

- “Targeted Education and Outreach” such as: “healthcare practitioner letters;” “patient labeling such as medication guides and patient package inserts;” and “training programs for healthcare practitioners or patients.”
- “Reminder Systems” such as: “patient education that includes acknowledgment of having read the material and an agreement to follow instructions;” “enrollment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.”
- “Performance-Linked Access Systems” such as: “product dispensing limited to pharmacies or practitioners that elect to be specially certified; product dispensing only to patients with evidence or other documentation of safe-use conditions (e.g., lab test results)”

These suggestions can be mapped directly onto the suggestions made for REMS in the 2007 amendments. In fact, as of the advent of the amendments, there were about 30 drugs that were approved with riskMAP restrictions (Kennedy).

### *2006 IOM Report*

In 2005, at the request of the FDA, the Institute of Medicine (IOM) conducted a study of the FDA's safety system and published the results in a 2006 report entitled, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. In this report, the IOM highlighted several factors and made several recommendations that would clearly later influence the REMS legislation. First, the IOM report noted that while clinical trials were well-designed for testing the efficacy of drugs, they were not well-designed to test drugs' safety saying "[t]rials designed to test hypotheses about serious safety outcomes would in most cases require many more subjects than are needed for an efficacy endpoint" (Institute, p. 106). The committee further noted that clinical trials were also not well-suited for detecting rare events (Institute, p. 106).

They further claimed that unfortunately a lot of data about drugs' effects would only emerge after approval (Institute, p. 107). The committee also indicated that to correct this problem by trying to create clinical trials that effectively reached these goals would be illogical because it would "require an unreasonable number of premarketing studies and would have serious implications not only for pharmaceutical companies in terms of research and development but also for patients awaiting new and important medicines" (Institute, p. 122). Thus the IOM recognized the fact that certain characteristics of drugs could only be realized in the post-approval stage.

Given these realities, instead of attempting to revise pre-approval clinical trials, the IOM committee recommended that the FDA adopt an ongoing approach to drug review saying:

The committee's vision of a transformed drug safety system has at its core a lifecycle approach to drug risk and benefit .... For FDA, attention to risk and benefit over a drug's lifecycle would require continuous availability of new data and ongoing, active reassessment of risk and benefit to drive regulatory action (responsive to the accumulating information about a given drug), and regulatory authority that is strong both before and after approval. (p. 4)

Thus the IOM report recommended ongoing surveillance of drugs after approval, a continual reassessment of the risk / benefit ratio, and increased FDA authority in the post-approval stage.

The FDA responded to the IOM report in a report by pledging to make several changes to their risk assessment system including the following which is relevant to the REMS legislation:

- Developing and incorporating new quantitative tools in the assessment of benefit and risk
  - Developing and validating risk management and risk communication tools
- (Response)

The IOM's report and the FDA's response to it clearly implicate the later REMS legislation.

### *Risk Management Plans and RiskMAPs*

Thus, the FDA has had a long history of conducting the kind of risk-benefit analysis that the REMS legislation of 2007 requires. Ever since the 1962 amendments,

the FDA has recognized that no drug was without benefit or risk; the goal of drug safety was to balance the benefits and risks to determine relative safety. Further, within the last decade, the FDA had made several innovations in regard to risk analysis. The 1999 Task Force on Risk Management recommended heightened post-market surveillance and more FDA sponsored studies. Later in 2001, the FDA developed Risk Management Plans which contained goals and objectives for drug companies in an effort to mitigate the known risks of their drugs. The later riskMAPs of 2004 were similar though arguably more refined in that the companies outlined strategies to target their drugs to the sub-populations where they would be the most effective. Then in 2006, the IOM report suggested that the FDA have a “lifecycle” approach to drug surveillance with risk assessment plans that could adjust based on new safety information. Thus, by the 2007 amendments, the FDA and its assessors had already experimented with several risk management devices that focused on post-market surveillance yet the FDA had limited statutory power to force companies to engage in recommended practices in the post-approval stage.

### **Major Recent Drug Occurrences that Implicated FDA’s Risk Analysis**

#### *Alosetron (2000)*

Several infamous drug incidents have shaped FDA’s risk assessment approach since its inception. Two recent events are the Alosetron and Vioxx crises. The Alosetron crisis of 2000 implicated the effectiveness of FDA’s then current risk assessment approach. Alosetron was a medication used to treat Irritable Bowel Syndrome developed by GlaxoSmithKline (Andresen, p. 287). FDA approved Alosetron in 2000 after trials

that found that Alosetron modestly helped relieve the pain of sufferers of Irritable Bowel Syndrome – particularly female patients with diarrhea-predominant IBS (Andresen, p. 288). Also, according to those trials, the only real side effect of Alosetron was constipation in mostly female patients (Andresen, p. 287). Thus the drug had a modest benefit with modest risks. However, after the drug was marketed, serious adverse effects appeared such as severe constipation and even death (Andresen, p. 288). Thus, GlaxoSmithKline (GSK) voluntarily withdrew Alosetron from the market (p. 288). However, after the withdrawal, former consumers of the drug lobbied the FDA and GSK protesting the loss of their drug.

To respond to these concerns, the FDA formed a special advisory committee to determine if the drug could return to the market (Andresen, p. 288). It was clear from the statements of members of this committee that the focus of the Alosetron hearings was on the risk-benefit ratio of the drug i.e. were its benefits worth its risks (Moynihan). As a result of these hearings, Alosetron was put back on the market with restrictions under a risk management plan in June 2002 (p. 288). At the time, Alosetron was historical because it was the first time that a drug had been withdrawn and then returned to market (Andresen, p. 288).

In a report of GSK and the FDA's Division of Gastrointestinal and Coagulation Drug Products to the Drug Safety and Risk Management Advisory Committee about Alosetron, the FDA noted that the goals of the risk management plan were to:

1. "Limit[] use to a subpopulation of patients in whom the benefits exceed risks"

2. “Inform[] patients and physicians of the risks and benefits of Lotronex (Alosetron) so that they can make informed decisions”
3. “Limit[] use of the drug to physicians who can manage severe diarrhea-predominant irritable bowel syndrome and adverse events associated with Lotronex (ischemic colitis and severe complications of constipation)”
4. “Hav[e] an on-going program evaluation to ensure goals are met” (Update, p. 1)

The restrictions outlined by the plan included revised detailed labeling, patient and physician registries for adverse event reporting, physician certification for use of the drug, and post-marketing commitments from GSK to continue clinical research on specific aspects of the drug (Update p. 2). Arguably the most significant restriction placed on Alosetron was that the drug was limited to a small group of patients, namely women with severe diarrhea-predominant IBS for whom other treatments had proved ineffective (Andresen, p. 289). According to the report, since the restrictions, there had only been 8 reported cases of adverse effects— none of them were deaths (Update, p. 1). However, some of the reported conditions were serious including one that required surgery to correct (Wolfe).

#### *Vioxx (2004)*

At the time that the 2007 amendments were being drafted probably no other drug occurrence was as synonymous with drug safety failure as Vioxx, the arthritis medication developed by Merck. The FDA approved Vioxx in May 1999 (House Committee, 2005).

Less than a year later (March 2000), Merck uncovered evidence that Vioxx had a greater association with heart attack than one of its competitor drugs, naproxen in the VIGOR (Vioxx Gastrointestinal Outcomes Research) study. An FDA advisory committee raised concerns about Vioxx a year and half later (House Committee, 2005). Then in 2004, in another clinical trial, Merck found a greater incidence of heart attacks among patients taking Vioxx than those patients taking the placebo. With that information, Merck pulled Vioxx off the shelves. After Merck removed Vioxx, the FDA made labeling requests to the other Cox-2 inhibitor drugs such as Celebrex and Bextra (House Committee, 2005).

Vioxx's importance in understanding the current 2007 amendments is made clear from the fact that right before the amendments were developed in 2005, a House committee held a hearing to determine the appropriateness of the FDA response during the Vioxx crisis. At the hearing, several FDA officials testified. Dr. Galson, Director of the Center for Drug Evaluation and Research (CDER) within the FDA, defended the FDA's handling of the situation saying the "FDA will only approve a drug after a sponsor demonstrates that its benefits outweigh its risks ..." (House Committee, 2005). He noted that the post-market phase generally lead to the detection of formerly unknown characteristics of drugs. He also noted that the FDA required drug companies to submit all data on adverse events that happened in the post-approval stage (House Committee, 2005). Dr. Galson also maintained that the FDA routinely conducted a cost benefit analysis whenever it received data on adverse reactions to a post-market drug including: "the frequency of the reports, the seriousness of the diseases or conditions for which the drug provides a benefit, the availability of alternative therapy and the consequences of not treating the disease" (House Committee, 2005). Further, according to Galson, at the



time of the hearing, the FDA was already making changes based on the Vioxx outcome including sponsoring the Institute of Medicine audit of its drug safety system, establishing a drug safety oversight board, and publishing advisories for pharmaceutical companies on risk management (House Committee, 2005).

During the hearing, there was, however, considerable criticism of the FDA from the House members. For instance, Congressman Waxman noted several FDA missteps in the FDA's response to the Vioxx crisis. First, FDA took two years to require the addition of cardiovascular risks to the Vioxx label. Second, FDA took three years to conduct an epidemiological study of the safety of Vioxx (House Committee, 2005). Third, the FDA never required Merck to do a cardiovascular safety study of Vioxx. Fourth, it was not until eleven months after VIGOR that an FDA advisory committee recommended that doctors be informed about the results of the study. Overall, the committee found that one of the causes of the poor FDA response to the Vioxx debacle was that there was a lack of communication between the office of New Drugs and the Office of Drug Safety (both part of CDER – Center for Drug Evaluation and Research) within FDA (House Committee, 2005). Also several congressman expressed consternation at the fact that the FDA did not have clear authority to require that pharmaceutical companies conduct clinical trials after approval except in limited cases (House Committee, 2005).

#### *Alosetron and Vioxx*

The Alosetron and Vioxx scandals were just a couple of the events that set the stage for the 2007 Amendments. The Alosetron occurrence was the first time that a drug was taken off the market for excessive risks and then replaced with limitations that the

FDA outlined. Thus it was historical in regard to FDA's risk analysis since the FDA had to engage in a careful balancing of the specific risks and benefits of a particular drug with infamous side effects. The Vioxx crisis then highlighted many of the challenges that the FDA faced in the post-approval stage. As news of the debacle surfaced, many were shocked at how little actual enforcement power the FDA had. The 2007 amendments, in regard to risk assessment, represented the attempt of the Congress to address the public concerns raised by drugs like Vioxx while achieving the balancing that was possible in drugs like Alosetron.

### **FDA's Policies Pre 2007**

In 2007, a record low number of drug applications were approved by the FDA. The FDA approved 17 new molecular entities (NMEs) and 2 biologic license applications (BLAs) (Hughes, p. 107). Several insiders had complained that this decrease was a result of the FDA's increased concern over risks because of controversies like Vioxx, a concern which has offset their risk-benefit analysis (Hughes, p. 107; Koski, p. 25). Hughes' article indicated that there may be a number of factors which affect the FDA's assessment the risks and benefits of new drugs. He noted that, on one hand, the FDA tended to require a lot more data for novel drugs because they were unfamiliar with them thus putting extra weight on the risks side of the analysis of these drugs (Hughes, p. 107). On the other hand, he also noted that if the new drug treated an ailment that was untreated before, its benefits could be weighted heavily (Hughes, p. 107).

In keeping with Hughes' analysis, nine of the 17 NMEs and the two BLAs that were approved had priority review status which meant that they were considered to be

significant advancements in a field (Hughes, p. 107). This fact suggested that, right before the 2007 amendments, the FDA was leaning more toward approving drugs that represented giant leaps forward as opposed to drugs that were simply incremental changes over predecessors. One pharmaceutical insider noted that drugs for infectious diseases and cancer were being approved more recently because, given the lack of alternative treatments, the benefits were so high that more risk could be tolerated (Hughes, p. 107). Yet there were also several drugs that many insiders expected the FDA to approve in 2007 that had not received approval including a prostate cancer vaccine (Provenge), an obesity drug (Acomplia) and a diabetes drug (Galvus) (Hughes, p. 107). Both Acomplia and Galvus were approved in the EU in 2007 (Hughes, p. 108).

On another issue, Young noted the criticism that the FDA had a tepid post-market surveillance system just prior to the 2007 amendments; companies had to conduct post-market research but the FDA had no enforcement power if they did not (Young, p. 1485). The Department of Health and Human Services Office of Inspector General conducted a report on the FDA's post-market surveillance and found a lack of compliance. According to the report, 35% of the 336 annual reports of drug companies were either missing or contained no information about post-market trials (Young, p. 1485). Thus, prior to the advent of the 2007 amendments, there was evidence that the FDA was limiting approval of new drugs and was unable to garner effective post-approval compliance from drug companies.

### **The 2007 Amendments**

The 2007 amendments were enacted on September 27, 2007 with multiple changes including the initiation of Risk Evaluation and Mitigation Strategies (REMS) in section 505-1. Looking at the plain language of the text raises numerous questions about the law's potential interpretation. According to the statute, a REMS, could be required for a drug at either the initial approval of a drug or in the post-approval stage.<sup>1</sup> According to the statute, the decision to require a REMS is made by the secretary of the FDA in consultation with the office responsible for reviewing the drug initially and the office responsible for post-approval safety.<sup>2</sup> At the initial approval stage, the law notes the factors that the FDA considers in determining which drugs will require a REMS. Those factors are:

- a. "Estimated size of the population likely to use the drug involved.
- b. The seriousness of the disease or condition that is to be treated with the drug.
- c. The expected benefit of the drug with respect to such disease or condition.
- d. The expected or actual duration of treatment with the drug.
- e. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population to use the drug.
- f. Whether the drug is a new molecular entity.”<sup>3</sup>

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<sup>1</sup> 505-1(a)(1) – (2)

<sup>2</sup> 505-1(a)(1)

<sup>3</sup> 505-1(a)

Though the law includes this list of factors, it does not give guidance on how the balance will tip based on these factors. These factors just seem to be the factors that the FDA would generally consider in their benefit-risk assessment of any new drug. They provide little direction for a company wondering whether its new drug will need a REMS or not. For instance, does a drug which reaches a large population tend to lead to a greater or lesser likelihood that a REMS will be required? Is a drug with a long duration of treatment more likely to require a REMS than one with a short duration? And what does the fact that it is a new molecular entity suggest?

Though not clearly spelled out, other FDA policies suggest answers to these questions. Some of these factors appear to be part of a benefit assessment, others seem part of a risk assessment, and some could be interpreted either way. For instance, in regard to the size of the population likely to use the drug, that could be an indication of the drug's benefit – the greater the number of people who can benefit from the drug, the greater the benefit and thus possibly the less likely that it would require a REMS. But then again, the greater the number of people affected by the drug, the greater the risk of more widespread harm from adverse events. This could thus be a risk assessment that cuts the other way; the greater the population, the more likely for the requirement of a REMS.

The seriousness of the disease or condition seems to be a calculation of benefit. The more serious the condition, the greater the benefit in having the drug, thus the more likely that it will not get an REMS. The same can be said of the expected benefit of the drug – the greater the benefit, the less likely for a REMS. The duration of treatment seems to be a risk assessment; since pre-approval clinical trials are generally limited in

their duration, it is difficult to predict the real effects of the drugs on the population when the drug is used for an extended period of time. Thus, possibly the logic is that the greater the duration of the treatment, the greater the risk and the more likely that they will be required to have a REMS.

The seriousness of the adverse incidents also seems to be a risk factor. The background incidence of the adverse events in the population also arguably assesses risk; if there is a high incidence of the adverse event in the population generally, it will make it more difficult to detect if the drug caused any increase in the incidence among that population (Hampton, p. 413). The fact of whether or not it is a new molecular entity seems to be able to cut both ways. On one hand, the FDA wants to encourage innovative drugs as opposed to “me too” drugs (Hughes, p. 107), thus the fact that it is a new molecular entity could be seen as a great benefit and less likely to result in a REMS. On the other hand, the fact that it is a new molecular entity also means that the FDA would most likely be unfamiliar with it and thus it is seen as higher risk and therefore more likely to require a REMS (Hughes, p. 107). All of this is speculation since the law does not give clear guidance on how the factors affect the choice of whether or not a REMS is required.

The only further guidance found in the law is the vague statement that the REMS will be required if it “is necessary to ensure that the benefits of the drug outweigh the risks of the drug” (p. 205, 505-1(a)(1)). On its face, this statement, like the factors, seems to just state a general FDA principle about drug assessment. However, there may be great meaning in the use of the word “necessary.” This word suggests that the REMS is required in cases where the drug is questionable – possibly a high risk drug – such that

the REMS is *necessary* to approve it. The challenge with that interpretation of the phrase is that it leads to the obvious question: if the drug's risks are so high that the benefits do not clearly outweigh the risks such that a REMS is *necessary*, then why is the FDA approving the drug at all? One could easily make the argument that the best thing for the FDA to do in that case is to not approve the drug.

Two questions then arise: what differentiates a drug that is rejected from one approved with a REMS and what differentiates a drug that is labeled “approvable” from a drug that is approved with a REMS? In other words, what is the “approved with a REMS” status adding that the current statuses do not? One possibility is that the REMS status is for high risk, high benefit drugs; the risks are high but so are the benefits so the FDA wants to approve it but they are still leery. To designate the drug as “approvable” or to reject it could lead to the company scrapping the project entirely. But the REMS will put the product on the market with further limitations.

The later discussion of the factors that lead to the requirement of a REMS for a post-approval drug does shed some light on what the FDA would consider for the initial approval. According to the statute, the FDA can require a REMS for a drug that initially did not need one if the FDA “becomes aware of new safety information” which makes it “necessary to ensure that the benefits of the drug outweigh the risks of the drug.”<sup>4</sup> In the statute, “new safety information” means data about a risk that has arisen since the drug was approved or information that calls the adequacy of the current REMS into question.<sup>5</sup> Then again, it raises the question of why not just take the drug off the market (or request that the company do so)? What it is about a drug that would make it problematic enough

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<sup>4</sup> 505-1(a)(2)(A)

<sup>5</sup> 505-1(b)(3)

for the FDA to want to do something about it but not enough to remove it from the market or insist that the company do so?

This question is further complicated by the phrasing in 505-1(d)(4)(C) where it states that the assessment requirement can be eliminated after 3 years if “serious risks of the drug have been adequately identified and assessed and are being adequately managed.” Thus, this section indicates that the FDA is contemplating using the REMS as a means to monitor drugs that have “serious risks” that the FDA is not confident are being “adequately identified[,] ... assessed[,] ... and managed.” Thus, the FDA is contemplating REMS for high risk drugs that one would assume have significant enough benefits to warrant exposing them to the market. This description could theoretically encompass an Alosetron or Vioxx. These are both drugs with known risks that are considered highly beneficial to certain patients. But given the language of the law, it may encompass a larger class of drugs for which the risks not just those that have known risks but also those that have risks that are unknown (i.e. not “identified”).

In section 505-1(f), the law indicates guidelines for “drugs with known serious risks.” This section could be the category of drugs being discussed in 505-1(a)(2) or a subset of them i.e. drugs that are beyond just risky and with unknown effects. For these drugs, the risks are defined as “serious”<sup>6</sup> which is a risk of a serious adverse drug experience which includes an experience of:

- 1) “Death”
- 2) “Immediate risk of death”
- 3) Inpatient or prolonged hospitalization

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<sup>6</sup> 505-1(f)



- 4) “Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions”
- 5) Birth defect
- 6) Requires a medical or surgical intervention to prevent any of the above occurrences<sup>7</sup>

The law contemplates that these highly dangerous drugs will still make it to market but with many safeguards such as:

- Training or special certification for health care providers on how to use the drug
- Certification for facilities that dispense the drug
- Limitations on the health care settings that can dispense the drug
- Limitations on the kind of patients who can get the drug (i.e. the most serious)
- Monitoring of patients who receive the drug
- Enrollment of all patients who receive the drug in a registry<sup>8</sup>

Further, the REMS is supposed to contain a timetable which includes assessments that occur at a least at the year and half mark, at the 3 year mark and at the 7 year mark – which can be terminated at the 3-year mark if the secretary so determines.<sup>9</sup> The REMS can include any of the following:

- Medication guide

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<sup>7</sup> 505-1(b)(5)

<sup>8</sup> 505-1(f)(3)

<sup>9</sup> 505-1(c) – (d)(1-4)

- Patient package insert
- A communication plan for health care providers which can include: a letter to the health care providers, a method of disseminating information about the REMS to health care providers including through professional societies<sup>10</sup>

Though it is not absolutely clear from the law, the REMS requirement was meant to be able to include various other parts of the law including limits on advertisements. Kennedy describes this in his public description of the bill saying:

- Post-approval registries or epidemiological studies to assess signals of serious risks or to screen for serious risks in expanded patient populations, or, when necessary, clinical trials to assess signals of serious risks;
- Pre-clearance of advertising, specific disclosures in advertising, or a prohibition on DTC advertisements for no more than 2 years after approval when disclosures alone aren't adequate to protect public health;
- Restrictions on distribution and use for a drug that presents a serious risk to the public health but offers significant benefit to patients. (Kennedy)

There are several administrative aspects of the REMS decision including a description of how REMS are modified<sup>11</sup> and a plan of dispute resolution.<sup>12</sup> Thus, the plain language of the law notes that there are a number of means that the FDA has to address safety concerns raised after approval but it is unclear what would be the factors that would cause the FDA to require a REMS versus simply disallowing the high risk drug.

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<sup>10</sup> 505-1(e)(1-3)

<sup>11</sup> 505-1(g)(4)

<sup>12</sup> 505-1(h)(4-5)

**Potential effect of 2007 amendments on companies**

There are several means through which we can consider what the effect of this law will be on drug safety. One clue to what the law could accomplish what the writers and signers of the law intended for it to accomplish i.e. the progress of the law through Congress. In describing the 2007 amendments upon the president's signing them into law, The White House Office of Communication noted that the act:

[R]eauthorize[s] a number of Food and Drug Administration programs including the Prescription Drug User Fee Act and Medical Device User Fee And Modernization Act; extends and modifies authorities related to pediatric uses of drugs and medical devices; and expands current authority related to post marketing surveillance of drugs. (White House)

It was similarly described in the Congressional record. There, in introducing the bill in the House through the Committee on Energy and Commerce and then to the whole House, Congressman Dingell coined H.R. 3580 as:

A bill to amend the Federal Food, Drug and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes. (Congressional Record H10551-04 & H10624-02)

Thus, the president and the sponsoring House member depicted the bill as a reissuing of the FDCA as well as an opportunity to increase the post-market authority of the FDA.

Thus, these national leaders viewed the REMS initiative as a way to increase the FDA's authority over drugs on the market. The agreement to pass the bill was passed in the House with 405 yeas and 7 nays. Thus, this bill had overwhelming support in the House. This broad support suggests that the writers believed themselves to be on solid ground

with the interests of the public i.e. expanding the enforcement power of the FDA to ensure safer drugs on the market (Congressional Record D1223-01).

There is further evidence about the way that the drug was perceived by lawmakers from the comments on the congressional floor. In introducing the bill in the Senate, Kennedy claimed that it was a “new way to oversee drug safety that is flexible enough to be tailored [to] the characteristics of particular drugs, yet strong enough to allow decisive action when problems are discovered” (Congressional Record S11831-01). Thus, he depicted the bill as a balancing between drug availability and drug safety. He elaborated on this further on the second day of comments saying:

[The bill] is a strong and comprehensive measure to improve the safety of the medicines we rely on ... [a]t the heart of our proposal is a new way to oversee drug safety that is flexible enough to be tailored [to] the characteristics of particular drugs, yet strong enough to allow decisive action when problems are discovered. For drugs that pose little risk, these actions might be as simple as a program to report side effects and a label with safety information – items that are currently required for all drugs. Drugs that raise major potential safety concerns might require additional clinical trials, a program to train physicians in using the drug safely, or a requirement that the prescribing physician have special skills. (Congressional Record S11937)

Thus, Kennedy appeared to be suggesting a nuanced approach to risk-benefit assessment on drugs. The goal of the law appeared to be to give the FDA tools to allow drugs to remain on the market to the extent that they are more helpful than harmful to certain sub-populations.

Senator Enzi similarly discussed compromise saying:

The FDA’s choice before was to pull a drug off the market or to leave it on. If it had some kind of a problem that could be soled some simple way, it wasn’t an option; pull it off or leave it on. We gave them a toolbox, a whole bunch of different things that they can now do so that drugs will be approved faster, and then when that clinical trial that we call the whole population of the United States kicks in, there is a mechanism for following all of those and finding small samples of problems, solutions to those small samples of problems, and the drug

that is working for people across this Nation doesn't have to be pulled off the market. It can still work for people who aren't affected by an adverse reaction. (Congressional Record S 11937)

In fact, Senator Enzi's comments depict the law as a way to keep drugs on the market not to take them off. He is suggesting that this law will give the FDA the means to tailor drugs like Vioxx to the narrow populations that can use them effectively.

Senator Enzi, however, in other remarks, stressed that the law was largely about increasing the FDA's enforcement power to ensure the safety of drugs. He noted that "the changes made in the drug safety components of this legislation are critical to restoring peace of mind to Americans who want to be assured that the drugs they purchase to treat illnesses and chronic medical conditions can be relied upon and trusted" (Congressional Record S11831-01). He further stated:

This bill gives FDA a full toolbox of options for dealing with potential safety problems, even if they are discovered after a drug is first marketed. FDA will be able to proactively react to additional safety information whenever that safety information is discovered, even after the drug is on the market. FDA will have the ability to identify side effects through active surveillance, and the authority to request a study or clinical trial to learn more about a potential safety problem. But perhaps most significantly, FDA will be able to obtain timely label changes in response to that safety information. (Congressional Record S11831-01)

Therefore, Senator Enzi also presented this legislation, including REMS, as a major increase in the FDA's enforcement. Senator Hatch similarly claimed that the bill was expansive saying that it represented a "new and enhanced mechanism for the prompt consideration of new safety-related information and sets forth strict timelines for the evaluation of such new data" (Congressional Record S11831-01). In her remarks, Congresswoman McCollum also referred to the bill as "significantly increas[ing] penalties for companies that violate safety standards" (Congressional Record E1983-03).

Many of the Senators, such as Dodd, Burr and Alexander, focused on the FDA's enhanced ability to require updated labeling when new safety information arose (Congressional Record S11831-01, S12050-02). Dodd noted "[f]or too long, the pressure on FDA to approve drugs has outweighed the necessity to have a systemic, unbiased review of the post-market safety of drugs whereby the FDA can take swift action should new safety information arise" (Congressional Record S11831-01). Dodd also referred to the Vioxx, Ketek, Avandia controversies and depicted this bill as a response to those failures (Congressional Record S11831-01).

However, in discussing REMS specifically, Burr noted that it really adds no new authority to the FDA. He noted that the FDA already uses riskMAPs which he views as the same as REMS (Congressional Record S11831-01). He frankly stated "[n]ow Risk Map regulations, which have never been studied for their effectiveness, are becoming law. It means more paperwork, deadlines, and checkpoints for drug companies, with no guarantee that it will improve patient safety. I do not support regulation for the sake of regulation" (Congressional Record S11831-01).

On the other hand, Republican Senator Coburn thought that the REMS legislation could be extremely significant. He urged that the FDA use its new REMS authority cautiously by making sure that the agency did not interfere with or impede drug distribution without there being clear evidence that there was a true risk. He urged a "measured assessment of risk vs. benefit in the intended patient population" (Congressional Record S11831-01). He further stated:

This legislation is a very delicate balancing act. No drug is completely safe-otherwise a doctor's prescription wouldn't be needed-but we do have to ensure that lifesaving medicines are able to get to patients. New authorities in the area of Risk Evaluation and Mitigation Strategies, REMS, labeling, and postmarket

commitments should not be taken lightly. These new authorities we are giving the FDA need to be used based on a measured assessment of risk vs. benefit in the intended patient population. For instance, labeling changes should only be undertaken when reliable data clearly shows safety problems that are not already reflected in the drug's label .... Another new authority granted to the FDA in a REMS is possible restrictions on distribution and use. If used, this restriction has the potential to impede patient access to important therapies and therefore should not be imposed where less burdensome approaches are available .... We absolutely need FDA to have all the tools necessary to ensure the safety and efficacy of drugs, but doctors need tools as well, and one of those important tools is new drugs on the market. (Congressional Record S11831-01)

He also supported the language in the law about a “less burdensome approach” so that manufacturers would be allowed to dialogue with the FDA about the best reaction to new safety data” (Congressional Record S11831-01).

Thus, though the Senators and house members often portray the 2007 amendments as a get “tough on drug companies” law – much of the language on the debating floor was about compromise and balancing. The REMS may then just be another manifestation of the FDA’s balancing between getting new drugs to market and ensuring the safety of the drugs. Thus, drug companies may experience the REMS changes as just more of the same – with little impact on their interaction with the FDA except for more paperwork to sign.

There is further support for this position in the article of Margaret Gilhooley. In her article, “Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, Preemption, and the Drug Reform Legislation,” Gilhooley notes that though the new laws give the FDA express authority to require tests and new labels but the FDA will have to engage in the lengthy process of making regulations for the dispute resolution procedures that are a part of those powers (Gilhooley, pp. 350-1). Gilhooley sees other limitations on the FDA’s use of the REMS. First, the FDA must determine that active postmarket

surveillance would not be sufficient to address the risks before it can require its own additional testing. Similarly, the agency must find that regular trials are insufficient before requiring additional clinical trials (Gilhooley, p. 351). Further, Gilhooley notes that though the regulations require dispute resolution procedures, they are not specified in the law – they are to be determined by “regulation and guidance.” This means that the FDA authorities will have to write regulations to outline these procedures which will take years to construct (Gilhooley, p. 351).

## **Conclusion**

Thus given the history of risk assessment, the text of the law and the legislative history, four questions arise about the potential effect of the REMS legislation in the 2007 amendments:

- 1) Will the REMS make the FDA more nimble and responsive to drug safety needs?
- 2) Or will REMS just represent business as usual? Companies and the FDA have always conducted risk analyses – will this just be another way of codifying those risks? Will it just be a way of making transparent to the public what the FDA and drug companies have been doing all along while allowing congressional leaders to look tough on drug companies?
- 3) Will REMS become another means for the FDA to stifle drug innovation as after the 1962 amendments?



From the data outlined in this work, it appears that while law will certainly give the FDA more formal power to force drug companies to investigate and prevent risks, it seems unlikely that the initiation of REMS will lead to radically different behavior on the part of the FDA. Before the 2007 amendments, the FDA already had a device that was very similar to REMS, namely the riskMAPs. Arguably, the very same factors that would have caused the FDA to require a riskMAP for a drug would lead to the requirement of a REMS.

Further, though the FDA had limited formal authority to require drug companies to initiate studies and change labels before the 2007 amendments, the FDA certainly had strong informal power. Drug companies, even before this new formal authority, were very much interested in being positively viewed by the FDA. The drug companies who did not comply with FDA requirements more did so because of a lack of FDA oversight than a lack of respect for the FDA. Prior to the 2007 amendments, the FDA certainly had enough coercive power to encourage companies to follow their recommendations where the FDA had no formal authority.

Further, the rationale behind REMS, as suggested by the comments of several congressmen and Senators, is really to balance the goals of making drugs safe and keeping beneficial though risky drugs on the market. This law seems consistent with the Alosetron event where the drug was allowed to return to the market with limits. Thus, though many of the congressional leaders claim that the law is meant to advance mainly safety, its actual wording also supports the interests of those who want risky drugs to be available to the populations that benefit from them.

Thus, it seems unlikely that the REMS legislation will lead to greater limitations on drug companies that will slow down approvals. The uproar over drug safety debacles such as Vioxx will continue the trend of the FDA toward a cautious approach to drug approval. But the REMS legislation will simply be another iteration of the FDA's ongoing attempt to ensure that companies balance risks and benefits. Instead of serving as a means to stifle benefits for fear of risks, the law would most likely result in drugs with significant risks being made available to the subpopulations that most need them.

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